KIR3DL2 contributes to delineate the Acute-type and is a therapeutic target in Adult T-cell leukemia/lymphoma

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INTRODUCTION

Adult T-cell leukemia (ATL) is a lymphoid neoplasm of CD4+ T lymphocytes caused by the human T-cell leukemia virus type I (HTLV-1), which is classified into 4 clinical subtypes (ie, smoldering, chronic, acute, and lymphoma).

Natural killer receptors (NKR) were previously identified on T-cell lymphomas1.

OBJECTIVES

Based on these new findings, we made the hypothesis that NKR could:
- be expressed on ATL cells and help to discriminate the different ATL forms,
- participate to the pathophysiology of ATL,
- serve as new therapeutic targets in this disease with a dismal prognosis.

RESULTS

KIR3DL2 PROTEIN EXPRESSION IS ASSOCIATED WITH ACUTE-TYPE ATL

ATL cells were identified by the low expression of CD3, CD4 and activation markers (CD25 and/or HLA-DR) and the absence of CD7 (Fig. 1A). KIR3DL2 was the only NKR that was expressed by CD4+ CD7- CD25+ ATL tumors cells (Fig. 1B). In 11/21 ATL patients, abnormal lymphocytes harbored heterogeneous KIR3DL2 expression by IHC (Fig. 1C). KIR3DL2 expression in acute ATL is confirmed by mRNA analysis (Fig. 1D). KIR3DL2 expression is associated with poorer survival in ATL (Fig. 1E).

In almost all acute ATL patients, abnormal lymphocytes harbored KIR3DL2 positivity (n=28/30, 93%). In contrast, lymphoma and chronic/smoldering cases were often negative for KIR3DL2 (n=2/8 and n=2/12 KIR3DL2+ respectively, p<0.001).

KIR3DL2 EXPRESSION CORRELATED WITH KIR3DL2 GENE PROMOTER HYPMETHYLATION

Upon 5Aza incubation, KIR3DL2 protein expression was efficiently induced with a dose-dependent effect on the cell surface of Hut 78 but not on Jurkat cells (Fig. 2B). Moreover, KIR3DL2 expression was not increased on primary PBMC from healthy donors and from 4 KIR3DL2+ ATL patients upon 5Aza treatment ex-vivo (Fig. 2C).

The KIR3DL2 promoter was significantly hypomethylated in acute ATL compared to lymphoma, chronic/smoldering types and HTLV-1 AC (p=0.0119, p<0.0001, and p<0.0001, respectively; unpaired t-test) that was consistent with KIR3DL2 expression (Fig. 2A).

REFERENCES


METHODS

Discovery cohort of 21 ATL patients

KIR3DL2 expression* (KIR3DL2+ ATL, KIR3DL2- ATL)

Flow-cytometry (Peripheral Blood)

50 ATL patients with 75 samples

55 peripheral blood samples

21 FFPB samples

IHC on frozen samples

Flow-cytometry (Lymph Node and PB)

30 acute-type ATL

8 lymphoma-type ATL

12 chronic/smoldering-type ATL

8 HTLV-1 carriers

HTLV-1 infection in-vitro

To explore the role of HTLV-1 on KIR3DL2 expression, KIR3DL2 and TAX mRNA expressions were assessed by prime-flow RNA assay on primary ATL cells and on activated CD4+ T cells that were infected with HTLV-1 in-vitro.

Ex-vivo autologous antibody dependent cell cytotoxicity (ADCC)

ADCC was performed on sorted primary ATL cells with IPH4102, a monoclonal anti-KIR3DL2 antibody that has shown robust clinical activity in Phase I in patients with relapsed/refractory advanced CTCL (NCT02593045).

HTLV-1, BUT NOT TAX ALONE, IS ABLE TO INDUCE KIR3DL2 EXPRESSION ON CD4+ T-CELLS

Purified HTLV-1 virions induced KIR3DL2 expression by CD4+ T-cells that was dependent on the quantity of HTLV-1 (p<0.03 equivalent, n=3; Fig. 3A). TAX mRNA was mostly expressed in KIR3DL2 positive CD4+ cells, while KIR3DL2 negative CD4+ cells were also negative for TAX mRNA (Fig. 3B).

Antitumor activity of IPH4102 against primary ATL cells was observed in all KIR3DL2 positive patient samples tested (n=3) and increased with the E/T ratio (Fig. 4). IC: isotype-matched control mAb. Moreover, IPH4102 did not mediate killing of KIR3DL2 negative ATL patient samples (n=5).

CONCLUSIONS AND PERSPECTIVES

1. KIR3DL2 expression is mainly associated with acute-type ATL.
2. Induction of KIR3DL2 gene transcription may be triggered by HTLV-1 infection followed by transcription maintenance due to DNA hypomethylation of the gene promoter.
3. The benefit of targeting KIR3DL2 by IPH4102 should be further investigated in ATL patients.